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Abstract: The aminophosphine-based pincer complexes [C6H3-2,6-NHP(piperidinyl)22Pd(Cl)] (2) and [C6H3-2,6-OP(piperidinyl)22Pd(Cl)] (3) are readily prepared from cheap starting materials by sequential addition of 1,1 ,1 -phosphinetriyltripiperidine and 1,3-diaminobenzene or resorcinol to solutions of [Pd(cod)(Cl)2] (cod = cyclooctadiene) in toluene under N2 in 'one pot'. Compounds 2 and 3 proved to be not only excellent catalysts for the Suzuki and the Heck cross-coupling reactions, but they are also very convenient to use: The toluene solutions of the 'one-pot' syntheses can be used directly for the catalytic reactions, thereby saving the time-consuming isolation of the catalysts. The Suzuki cross-coupling reaction catalyzed by 2 and 3 can be performed in air at 100 °C in toluene of technical quality: in the presence of only 0.001mol% of catalyst, several electronically deactivated and sterically hindered aryl bromides are quantitatively coupled with phenylboronic acid within a few minutes of reaction time. Furthermore, complex 2 enables the use of activated and non-activated aryl chlorides as coupling partners in the Suzuki reaction. Compounds 2 and 3 have also been shown to be highly active and reliable Heck catalysts: Very low catalyst loadings and short reaction times are required for the quantitative coupling of several electronically deactivated and sterically hindered aryl bromides with various olefins at 140 °C. At increased temperatures, even electronically deactivated and sterically hindered aryl chlorides can be efficiently coupled with olefins in the presence of only 0.01 mol% of catalyst.

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Aminophosphine Palladium Pincer Complexes for Suzuki and Heck Reactions

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Abstract: The aminophosphine-based pincer complexes [C_6H_3-2,6-{NHP(piperidinyl)$_2$}$_2$Pd(Cl)] (**2**) and [C_6H_3-2,6-{OP(piperidinyl)$_2$}$_2$Pd(Cl)] (**3**) are readily prepared from cheap starting materials by sequential addition of 1,1',1"-phosphinetriyltripiperidine and 1,3-diaminobenzene or resorcinol to solutions of [Pd(cod)(Cl)$_2$] (cod = cyclooctadiene) in toluene under N_2 in 'one pot'. Compounds **2** and **3** proved to be not only excellent catalysts for the Suzuki and the Heck cross-coupling reactions, but they are also very convenient to use: The toluene solutions of the 'one-pot' syntheses can be used directly for the catalytic reactions, thereby saving the time-consuming isolation of the catalysts. The Suzuki cross-coupling reaction catalyzed by **2** and **3** can be performed in air at 100 °C in toluene of technical quality: in the presence of only 0.001mol% of catalyst, several electronically deactivated and sterically hindered aryl bromides are quantitatively coupled with phenylboronic acid within a few minutes of reaction time. Furthermore, complex **2** enables the use of activated and non-activated aryl chlorides as coupling partners in the Suzuki reaction. Compounds **2** and **3** have also been shown to be highly active and reliable Heck catalysts: Very low catalyst loadings and short reaction times are required for the quantitative coupling of several electronically deactivated and sterically hindered aryl bromides with various olefins at 140 °C. At increased temperatures, even electronically deactivated and sterically hindered aryl chlorides can be efficiently coupled with olefins in the presence of only 0.01 mol% of catalyst.

Keywords: Aminophosphines · C–C coupling · Heck reaction · Pincer complexes · Suzuki reaction

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1. Introduction

Among the most efficient methods for carbon–carbon bond formation are the palladium-catalyzed Mizoroki-Heck[1] and Suzuki-Miyaura[2,3] cross-coupling reactions, which are nowadays indispensable tools in organic synthesis for the catalytic formation of symmetric and non-symmetric olefins or biaryls, respectively.

Since both of these palladium-catalyzed reactions typically use an aryl halide as one of the starting materials and couple it with either an olefin (Heck reaction) or an arylboronic acid (Suzuki reaction), particularly catalysts which are able to use deactivated and sterically hindered aryl bromides or even aryl chlorides as substrates are of high general interest.

In the last few years, many palladium catalysts for either reaction have been developed, but although some are able to couple sterically or electronically demanding aryl halides at very low catalyst loadings, their syntheses are often not only time consuming and difficult, but also require the use of expensive starting materials.[4–12] Most of these palladium catalysts suffer from other drawbacks as well, such as poor thermal stability as well as poor stability towards oxygen and water, a major problem especially for catalysts employed in the Heck cross-coupling reaction because a typical protocol for this reaction still requires prolonged reaction times at high temperatures in combination with relatively high catalyst loadings – all factors promoting the formation of palladium black and thereby leading to inactivation of the active species.

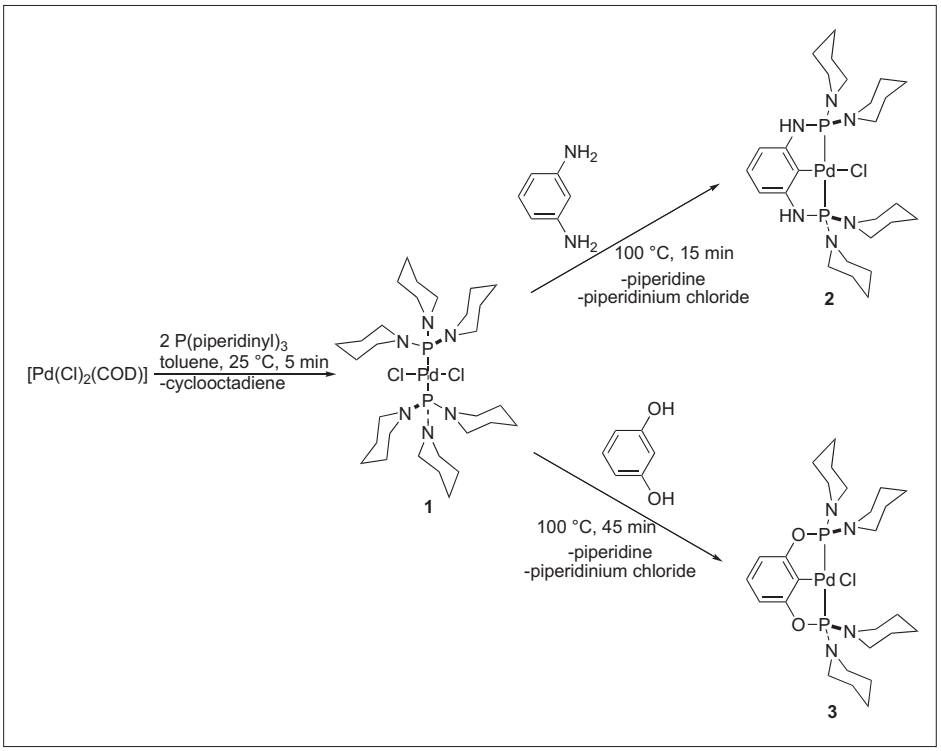
Pincer complexes of palladium are among the most efficient Heck catalysts and continuously attract attention because of their unique balance between stability and reactivity. Seemingly slight electronic and steric modifications of the pincer core and/or the phosphine substituents have been demonstrated to dramatically influence their catalytic activities.[4a,d,13,14] The successful application of pincer-type complexes in the Heck reaction considerably increased the interest in developing pincer-based Suzuki catalysts as well.[15–17] Ever since pincer-type complexes have been successfully introduced as highly efficient catalysts in the Heck reaction, it has been discussed whether a Pd^{II}/Pd^{IV} mechanism or the formation of palladium nanoparticles leads to their high catalytic activity.[4a,d] Nowadays, pincer complexes are in most cases considered as depot forms of palladium nanoparticles, but nevertheless, the involvement of Pd^{IV} intermediates in the catalytic cycle still cannot be excluded completely.[18,19]

Either way, the choice of aminophosphine pincer ligands might prove to be an advantage: Apart from their high σ-donor strength, aminophosphine ligands can donate additional electron density *via* the nitrogen lone pairs to the metal center, thereby making Pd^{IV} intermediates more

easily accessible. On the other hand, if palladium nanoparticles are the active species, pincer complexes should act as clean sources of palladium nanoparticles. Since aminophosphines should promote their formation, enhanced catalytic activity as well as shorter induction periods should be observed in comparison with their phosphine and phosphite analogues.

In comparison with many other palladium complexes used to promote the Mizoroki-Heck reaction or the Suzuki-Miyaura reaction, the aminophosphine-based palladium pincer complexes [C_6H_3-2,6-{NHP(piperidinyl)$_2$}$_2$Pd(Cl)] (**2**) and [C_6H_3-2,6-{OP(piperidinyl)$_2$}$_2$Pd(Cl)] (**3**) (Scheme 1) are not only readily prepared from cheap starting materials within a day, but they are also extremely efficient catalysts for either reaction: Very low catalyst loadings and short reaction times are required for the quantitative coupling of several electronically deactivated and sterically hindered aryl bromides with phenylboronic acid or various olefins. At increased temperatures, even electronically deactivated and sterically hindered aryl chlorides can be efficiently coupled with olefins in the presence of only 0.01mol% of catalyst.[14,15]

Mechanistic studies performed with **2** and **3** showed that the Suzuki cross-coupling reaction most probably proceeds *via* a Pd^{II}/Pd^{IV} mechanism,[15] while the Heck reaction was shown to be catalyzed by palladium nanoparticles, for which the aminophosphine-based palladium pincer complexes **2** and **3** apparently are ideal precursors.[14]



Scheme 1. Synthesis of the catalysts **2** and **3**.

2. One-pot Synthesis of the Pincer Complexes

Instead of synthesizing the pincer ligand separately in a first step and then reacting it with a suitable palladium precursor such as [Pd(Cl)$_2$(cod)] (cod = cycloocta-1,5-diene) to the desired complex, aminophosphine-based pincer complexes of palladium with the general formula [Pd(Cl)(C_6H_3-2,6-XP(piperidinyl)$_2$)$_2$] (X = NH, **2**, X = O, **3**) can be prepared by facile activation of C–H and P–N bonds. Their syntheses include the use of the readily prepared dichloro(bis(1,1',1''-(phosphinetriyl)tripiperidine))palladium complex (**1**) as a template for reactions with 1,3-diaminobenzene or resorcinol to build up the aromatic pincer core directly on the metal center, thus making the independent synthesis and purification of the air- and moisture-sensitive ligand systems unnecessary (Scheme 1).

Treatment of a suspension of [Pd(Cl)$_2$(cod)] in toluene under N_2 at room temperature with two equivalents of P(piperidinyl)$_3$ (which is easily prepared from phosphorus trichloride and piperidine) results immediately in a bright orange solution containing compound **1**. Addition of an equimolar amount of 1,3-diaminobenzene or resorcinol under nitrogen and stirring at 100 °C for 15 or 45 min, respectively, leads to the exclusive formation of compounds **2** and **3**. Although removal of the volatiles under reduced pressure and subsequent extractions with diethyl ether gives pure **2** and **3** in high yields, the isolation of the pincer complexes **2** and **3** is unnecessary for their application as catalysts in C–C cross-coupling reactions. The catalyst solutions of the one-pot syntheses can be used for catalytic reactions without purification and remain stable in solution for several months at room temperature.

Complexes **2** and **3** are thermally very stable. No visible decomposition was observed upon heating at 150 °C in NMP or xylene for a week. Toluene solutions of **2** or **3** remain stable at 100 °C in an oxygen atmosphere for more than a week. On the other hand, addition of a few drops of water to dioxane solutions of **2** or **3** at 100 °C results in partial palladium deposition after 24 h.

3. Catalytic Activity of the Pincer Complexes in C–C Cross-Coupling Reactions

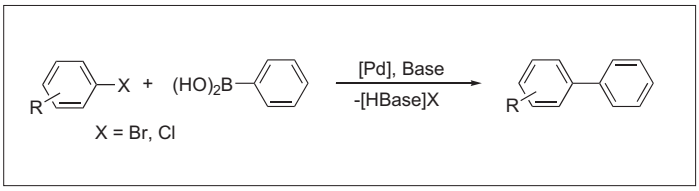
Compounds **2** and **3** proved to be not only excellent catalysts for the Suzuki-Miyaura and the Mizoroki-Heck cross-coupling reactions, but they are also very convenient to use: The toluene solutions of the 'one-pot' syntheses can be used directly for the catalytic reactions, thereby saving the time-consuming isolation of the catalysts. The resulting conversion rates and yields in the catalytic reactions are essentially the same as those of freshly prepared catalyst solutions from pure **2** and **3**, respectively.

3.1 *Suzuki Reaction*

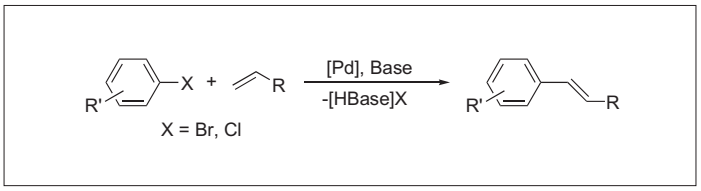
Complex **2** turned out to be an extremely efficient catalyst for the Suzuki–Miyaura cross-coupling reaction (Scheme 2) and led to very high reaction rates and yields in extremely short reaction times and with very low catalyst loadings (Table 1). Complex **3** generally shows significantly lower catalytic activities than **2**, but still is among the best catalysts reported up to date.[15]

As a consequence of the extremely high catalytic activities of **2** and **3**, the cross-coupling of aryl bromides with phenylboronic acid can be carried out in toluene of technical quality in flasks open to air. This is possible since biaryl formation is much faster than water-induced catalyst degradation.

Best results were obtained at 100 °C with toluene as solvent with K_3PO_4 as base in presence of 0.001 mol% of catalyst **2**. Under these conditions, phenylboronic acid was quantitatively coupled with activated, non-activated, and deactivated aryl bromides, such as 4'-bromoacetophenone, bromobenzene, and 4-bromoanisole,



Scheme 2. Suzuki-Miyaura cross-coupling reaction.



Scheme 3. Mizoroki-Heck cross-coupling reaction.

within less than 5 min (Table 1, entries 1, 4, and 6). Coupling reactions performed with 1,3-dibromobenzene yielded 76% 1,1':3',1''-terphenyl and 24% 3-bromobiphenyl after five minutes, while complete conversion into 1,1':3',1''-terphenyl was achieved after ten min (Table 1, entry 5). The activity of catalyst **2** decreased as sterically hindered substrates were used as coupling partners. While coupling reactions with 2-bromotoluene led to 83% conversions within 5 min , 62% conversion was obtained after 15 min using 2-bromo-*m*-xylene as the substrate (Table 1, entries 8 and 9). Similar conversions but longer reaction times were observed when catalyst **3** was used in place of catalyst **2** for the C–C coupling of phenylboronic acid with bromobenzene, 4-bromoanisole, or 3-bromo-*m*-xylene (Table 1, entries 3 and 7).

Reactions carried out with 4'- chloroacetophenone or chlorobenzene also showed high conversion rates in short reaction times (Table 1, entries 11–13). For example, complete conversions of chlorobenzene at 100 °C with 0.1 mol% catalyst **2** was observed after 90 min (Table 1, entry 11). In contrast, coupling reactions with deactivated or sterically hindered aryl chlorides were less successful and only led to approximately 10% conversions after 3 h (Table 1, entries 14 and 15).

Nevertheless, in most of the examples of the Suzuki–Miyaura cross-coupling reactions performed (in particular when aryl bromides as well as activated and unactivated aryl chlorides were employed), catalysts **2** (and to a minor extent **3**) were more efficient than the reference systems of $[Pd(Cl)(C_6H_3(NHP(Ph)_2)_2]$,[17] $[Pd_2(Cl)_2(C_6H_2(tBu)_2O)P(OR)_2)_2]$,[11g,h] and $Pd(OAc)_2/PCy_2Ar$.[3h] Comparisons with the extremely active air- and moisture-stable NHC-bearing $[Pd^{II}(Cl)(R\text{-allyl})]$ (NHC=N-heterocyclic carbene)[20] complexes are difficult, since the Suzuki reactions were generally performed at room temperature.[12k] However, because of the high conversions obtained within a few minutes and the facile syntheses of **2** and **3**, these systems belong to the most convenient Suzuki catalysts reported to date.

The Suzuki reaction is strongly influenced by the choice of the solvent and base, as well as the reaction temperature. For example, replacing toluene by NMP and/or K_3PO_4 by K_2CO_3 or Cs_2CO_3 led to a substantial drop in the reaction rate. Similarly, lowering the reaction temperature to 50 °C led to only 30% conversion after 12 h and 58% conversion after 24 h with 0.01 mol% of catalyst **2** while almost no activity was observed at room temperature.

Table 1. Suzuki cross-coupling reaction of aryl halides with phenylboronic acid catalyzed by $[Pd(Cl)(C_6H_3\text{-}2,6\text{-}(YP(piperidinyl)_2)_2]$ (Y = NH, **2**; Y = O, **3**)[a]

Entry	Aryl halide	Catalyst ([mol%])	Conv. [%][b]	*t* [min]	TOF[c]	TON[d]
1	bromobenzene	**2** (0.001)	100	5	1'200'000	100'000
2	bromobenzene	**2** (0.0001)	100	55	1'090'909	1'000'000
3	bromobenzene	**3** (0.001)	98	10	558'000	294'000
4	4'-bromoacetophenone	**2** (0.001)	100	4	1'500'000	100'000
5	1,3-dibromobenzene	**2** (0.001)	100	10	600'000	50'000
6	4-bromoanisole	**2** (0.001)	95	5	1'140'000	95'000
7	4-bromoanisole	**3** (0.001)	96	10	576'000	96'000
8	2-bromotoluene	**2** (0.001)	83	5	996'000	83'000
9	2-bromo-*m*-xylene	**2** (0.001)	62	15	248'000	62'000
10	2-bromo-*m*-xylene	**3** (0.001)	92	30	184'000	92'000
11	chlorobenzene	**2** (0.1)	99	90	653	980
12	chlorobenzene	**3** (0.1)	31	90	207	276
13	4'-chloroacetophenone	**2** (0.01)	92	90	6'133	9'200
14	2-chloro-*m*-xylene	**2** (0.1)	11	180	37	110
15	4-chloroanisole	**2** (0.1)	8	180	27	80

[a]Reaction conditions: 4.0 mmol aryl halide, 6.0 mmol $PhB(OH)_2$, 8.0 mmol K_3PO_4, 12 ml toluene (technical quality), catalyst (synthesized in 'one-pot' and used without purification) added in solution, reactions performed in air at 100 °C. [b]Determined by GC/MS, based on aryl halide. [c]Defined as mol product per mol of catalyst per hour. [d]Defined as mol product per mol of catalyst.

3.2 *Heck Reaction*

The aminophosphine-based palladium pincer complexes $[C_6H_3\text{-}2,6\text{-}\{NHP(piperidinyl)_2\}_2Pd(Cl)]$ (**2**) and $[C_6H_3\text{-}2,6\text{-}\{OP(piperidinyl)_2\}_2Pd(Cl)]$ (**3**) are also extremely efficient and reliable Heck catalysts (Scheme 3).[14]

Very low catalyst loadings and short reaction times are required for the quantitative coupling of several electronically deactivated and sterically hindered aryl bromides with various olefins (Table 2). At increased temperatures, even electronically deactivated and sterically hindered aryl chlorides can be efficiently coupled with olefins in the presence of only 0.01mol% of catalyst (Table 3).

As in the Suzuki cross-coupling, catalyst **3** is generally less active than **2** in Heck reactions performed with aryl bromides. For example, styrene and bromobenzene underwent complete C–C coupling in the presence of only 0.002 mol% of **2** and K_2CO_3 within 2.5 h in DMF at 140 °C, whereas a reaction time of 10 h was necessary with catalyst **3** (Table 2, entries 1 and 2). As demonstrated by the cross-coupling of styrene with the electronically deactivated 4-bromoanisole or the sterically hindered 2-bromotoluene, as well as the reaction of 4-methoxystyrene or 2-methylstyrene with bromobenzene, catalyst **2** offers two possible pathways to the same products, which are obtained in high yields and short reaction times by either way (Table 2, entries 5–9). Although a decrease in activity was observed with 2-bromo-*m*-xylene and styrene as substrates, nevertheless 95% conversion was obtained after 8 h (Table 2, entry 10). Heck reactions performed with N,N-dimethyl acrylam-

Table 2. Heck cross-coupling reaction of aryl bromides with various olefins catalyzed by [Pd(Cl)(C_6H_3-2,6-(YP(piperidinyl)$_2$)$_2$)] (Y = NH, **2**; Y = O, **3**)[a]

Entry	Aryl halide	Olefin	Cat. (ppm)	Conv. [%][b] (*cis*/*trans*/*gem*)	*t* [h]	TOF[c]	TON[d]
1	bromobenzene	styrene	**2** (20)	>99 (1/90/10)	2.5	19'880	49'700
2	bromobenzene	styrene	**3** (20)	96 (1/90/10)	10	4'800	48'000
3[e]	bromobenzene	styrene	**2** (0.2)	>99 (1/90/10)	36	138'333	4'980'000
4	1,3-dibromobenzene	styrene	**2** (20)	>99 (1/7/0/0)[f]	3.5	14'157	49'550
5	4-bromoanisole	styrene	**2** (20)	99 (0/10/1)	2.5	19'800	49'500
6	bromobenzene	4-methoxystyrene	**2** (20)	97 (0/10/1)	2.5	19'400	48'500
7	4-bromoanisole	styrene	**3** (20)	97 (0/10/1)	11	4'409	48'500
8	2-bromotoluene	styrene	**2** (20)	98 (0/20/1)	2.5	19'600	49'000
9	bromobenzene	2-methylstyrene	**2** (20)	90 (0/20/1)	2.5	18'000	45'000
10[g]	2-bromo-*m*-xylene	styrene	**2** (20)	95 (2/80/1)	8	2'375	19'000
11	bromobenzene	N,N-dimethyl acrylamide	**2** (20)	100 (1/20/0)	2	25'000	50'000
12	bromobenzene	N,N-dimethyl acrylamide	**3** (20)	100 (1/25/0)	10	5'000	50'000
13	2-bromotoluene	N,N-dimethyl acrylamide	**2** (20)	100 (1/40/0)	4	12'500	50'000
14	bromobenzene	*n*-butyl acrylate	**2** (50)	100 (1/100/1)	4.5	4'444	20'000
15	bromobenzene	*n*-butyl acrylate	**3** (50)	93 (1/100/0)	12	775	9'300
16	4-bromoanisole	*n*-butyl acrylate	**2** (50)	99 (1/100/0)	4.5	4'400	19'800
17	bromobenzene	*n*-butyl vinyl ether	**2** (50)	100 (4/3/2)	5	4'000	20'000
18	bromobenzene	*n*-butyl vinyl ether	**3** (50)	99 (4/3/2)	16	1'238	19'800
19[g]	2-bromo-*m*-xylene	*n*-butyl vinyl ether	**2** (50)	72 (5/3/5)	8	1'800	14'400
20[g]	bromobenzene	4-vinylpyridine	**2** (200)	100 (1/25/0)	8.5	589	5'000
21[g]	2-bromotoluene	4-vinylpyridine	**2** (200)	100 (1/20/0)	12	417	5'000
22[g]	bromobenzene	2-vinylpyridine	**2** (200)	53 (1/10/0)	60	44	2'650
23[h]	bromobenzene	(*E*)-stilbene	**2** (50)	98	20	980	19'600
24[h]	bromobenzene	1,1-diphenylethene	**2** (50)	99	24	825	19'800

[a]Reaction conditions: 4.0 mmol aryl halide, 4.4 mmol olefin, 4.4 mmol K_2CO_3, 5 ml DMF, catalyst (synthesized in 'one pot' and used without purification) added in solution (toluene), reaction performed at 140 °C under N_2 atmosphere. [b]Determined by GC/MS, based on aryl halide. [c]Defined as mol product per mol of catalyst per hour. [d]Defined as mol product per mol of catalyst. [e]2.0 mol aryl halide, 2.4 mol olefin, 2.4 mol K_2CO_3, 1 l DMF. [f]Product distribution refers to (*cis*–*trans*/*trans*–*trans*/*gem*–*trans*/*cis*-*cis*). [g]Reactions performed in NMP. [h]Reaction performed at 160 °C.

Table 3. Heck cross-coupling reaction of aryl chlorides with various olefins catalyzed by [Pd(Cl)(C_6H_3-2,6-(YP(piperidinyl)$_2$)$_2$)] (Y = NH, **2**; Y = O, **3**)[a]

Entry	Aryl halide	Olefin	Cat.	Conv. [%][b] (*cis*/*trans*/*gem*)	*t* [h]	TOF[c]	TON[d]
1[e]	4'-chloroacetophenone	styrene	**2**	100 (5/100/1)	2.5	4000	10000
2[e]	4'-chloroacetophenone	styrene	**3**	95 (0/1/0)	2.5	3800	9500
3[e]	4'-chloroacetophenone	N,N-dimethyl acrylamide	**2**	99 (0/1/0)	2.5	3960	9900
4[e]	4'-chloroacetophenone	N,N-dimethyl acrylamide	**3**	96 (0/20/1)	2.5	3840	9600
5	chlorobenzene	N,N-dimethyl acrylamide	**2**	77 (3/100/1)	16	481	7700
6	chlorobenzene	N,N-dimethyl acrylamide	**3**	91 (0/60/1)	16	569	9100
7	2-chloro-*m*-xylene	N,N-dimethyl acrylamide	**2**	57 (0/1/0)	28	204	5700
8	4-chloroanisole	N,N-dimethyl acrylamide	**2**	66 (0/1/0)	72	92	6600
9	chlorobenzene	4-methylstyrene	**2**	82 (1/80/10)	12	683	8200
10	4-chlorotoluene	4-methylstyrene	**2**	80 (1/7/0)	18	444	8000
11	chlorobenzene	4-methoxystyrene	**2**	90 (1/100/10)	18	500	9000
12	chlorobenzene	4-methoxystyrene	**3**	100 (1/100/10)	18	556	10000
13	4-chlorotoluene	4-methoxystyrene	**3**	98 (0/8/1)	18	544	9800

[a]Reaction conditions: 4.0 mmol aryl halide, 6.0 mmol olefin, 4.4 mmol K_2CO_3, 0.6 mmol tetrabutylammonium bromide, 5 ml NMP, 0.01 mol% of catalyst (synthesized in one pot and used without purification) added in solution (toluene), reaction performed at 200 °C under N_2 atmosphere. [b]Determined by GC/MS, based on aryl halide. [c]Defined as mol product per mol of catalyst per hour. [d]Defined as mol product per mol of catalyst. [e]Reaction performed at 160 °C.

ide exhibit very similar conversion rates and yields to those with styrene (Table 2, entries 11–13). Complete product formation and excellent selectivities but slightly lower conversion rates were observed with n-butyl acrylate as coupling partner (Table 2, entries 14–16). For instance, using deactivated 4-bromoanisole as substrate led to quantitative (97%) product formation within 4.5 h in the presence of only 0.005 mol% of **2**. Quantitative product formation but a further decrease in the conversion rates accompanied by low selectivity was observed after 5 h with 0.005 mol% of **2** with the electronically deactivated n-butyl vinyl ether (Table 2, entries 17–18). Even the sterically hindered 2-bromo-*m*-xylene was converted to 72% of product after only 8 h (Table 2, entry 19). When the amount of catalyst was increased to 0.02 mol%, 4-vinylpyridine for example undergoes quantitative coupling with bromobenzene and the sterically hindered 2-bromotoluene within 8 and 12 h (Table 2, entries 20 and 21). Significantly lower conversion rates were observed with 2-vinylpyridine (Table 2, entry 22), most probably due to chelation.

Furthermore, the exceptional high catalytic activity of **2** and its practical applicability was demonstrated in an exemplary 'large-scale' reaction, in which bromobenzene (210 ml; 2.0 mol) and styrene (250 ml; 2.4 mol) were quantitatively coupled in the presence of only 0.00002 mol% of catalyst within 36 h (Table 2, entry 3).

Additionally, raising the reaction temperature to 160 °C allows the use of disubstituted olefins, such as (*E*)-stilbene or 1,1-diphenylethene as coupling partners. For instance, 1,1',1''-ethene-1,1,2-triyltribenzene was quantitatively formed within 20 h on addition of 1.1 equivalents of bromobenzene to solutions of (*E*)-stilbene in DMF (Table 2, entry 23). Notably, the same product was formed quantitatively within 24 h under identical reaction conditions by either using 1,1-diphenylethene as substrate (Table 2, entry 24), or by adding 2.2 equivalents of bromobenzene to solutions of styrene in DMF.

In contrast to Heck reactions performed with aryl bromides, catalysts **2** and **3** show the same level of activity with aryl chlorides as substrates. In the presence of 0.01 mol% of catalyst and about 15% of tetrabutylammonium bromide in 1-methyl-2-pyrrolidone (NMP) at 160 °C, the electronically activated 4'-chloroacetophenone and N,N-dimethyl acrylamide or styrene were coupled almost quantitatively within 2.5 h (Table 3, entries 1–4). Increasing the reaction temperature to 200 °C, enabled even the coupling of nonactivated, deactivated, and *ortho*-substituted aryl chlorides with various olefins. For example, reactions performed with chlorobenzene and N,N-dimethyl acrylamide afforded the coupling product in 77% yield in the presence of catalyst **2** and in 91% yield with catalyst **3** after 16 h (Table 3, entries 5 and 6). Remarkably, even the sterically hindered 2-chloro-*m*-xylene was converted to about 60% of the product after 28 h in the presence of **2** with N,N-dimethyl acrylamide as coupling partner (Table 3, entry 7). A prolonged reaction time was required with the electronically deactivated 4-chloroanisole as substrate (Table 3, entry 8). A conversion of 82% was achieved within 12 h when chlorobenzene was coupled with 4-methylstyrene (Table 3, entry 9). Even higher conversions were observed after 18 h when chlorobenzene or 4-chlorotoluene were allowed to react with 4-methylstyrene or 4-methoxystyrene as coupling partners (Table 3, entries 10–13).

Overall, **2** and **3** belong to the most active and most convenient Heck catalysts reported up to date, since their catalyst solutions are readily prepared from very cheap starting materials in 'one pot' and can be used directly for catalytic reactions without purification. Catalyst **2** (and to a minor degree **3**) are more efficient in the majority of the coupling reactions performed with aryl bromides than many systems reported in literature.[4a,13a,21–23] although in some cases comparisons are difficult, since the Heck reactions were generally carried out at room temperature.[5b,6]Likewise, because of the wide span of reaction temperatures employed, the Heck reactions performed with aryl chlorides are nearly impossible to compare with other systems.[4d,5b,24]

4. Conclusions

In summary, a new concept for the short, facile and high yielding synthesis of complexes with the general formula [Pd(Cl)(C_6H_3-2,6-(YP(piperidinyl)$_2$)$_2$)] (Y = NH, **2**; or Y = O, **3**) has been developed.[15] Compounds **2** and **3** proved to be not only excellent catalysts for the Suzuki-Miyaura and the Mizoroki-Heck cross-coupling reactions, but they are also very convenient to use: The toluene solutions of the 'one-pot' syntheses can be used directly for the catalytic reactions, thereby saving the time-consuming isolation of the catalysts.

Due to the high catalytic activity of **2** (and to a minor extent **3**), the Suzuki reaction performed with aryl bromides can be carried out in toluene of technical quality in a flask open to air since biaryl formation is much faster than water-induced catalyst degradation.[15]

Compounds **2** and **3** have also been shown to be highly active and reliable Heck catalysts: Very low catalyst loadings and short reaction times are required for the quantitative coupling of several electronically deactivated and sterically hindered aryl bromides with various olefins at 140 °C. At increased temperatures, electronically deactivated and sterically hindered aryl chlorides can be efficiently coupled with olefins in the presence of only 0.01mol% of catalyst.[14] Further catalytic reactions performed with complexes **2** and **3** are in progress.

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[1] R. F. Heck, H. A. Dieck, *J. Am. Chem. Soc.* **1974**, *96*, 1133.

[2] N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20,* 3437.

[3] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95,* 2457; b) A. Suzuki in 'Metal-Catalyzed Cross-Coupling Reactions', Eds. F. Diederich, P. J. Stang, Wiley-VCH, Weinheim, **1998**, chap. 2; c) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; d) N. Miyaura, *Top. Curr. Chem*. **2002**, *219*, 11; e) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; f) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633; g) F. Bellina, A. Carpita, R. Rossi, *Synthesis* **2004**, 2419; h) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.

[4] a) M. Ohff, A. Ohff, M. E. van der Boom, D. Milstein, *J. Am. Chem. Soc.* **1997**, *119*, 11687; b) K. Kiewel, Y. Liu, D. E. Bergbreiter, G. A. Sulikowski, *Tetrahedron Lett.* **1999**, *40*, 8945; c) F. Miyazaki, K. Yamaguchi, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 7379; d) D. Morales-Morales, R. Redon, C. Yung, C. M. Jensen, *Chem. Commun.* **2000**, 1619; e) D. Morales-Morales, C. Grause, K. Kasaoka, R. Redon, R. Cramer, C. M. Jensen, *Inorg. Chim. Acta* **2000**, *300–302*, 958; f) S. Sjovall, O. P. Wendt, C. J. Anderson, *Chem. Soc. Dalton Trans.* **2002**, 1396; g) D. Morales-Morales, R. E. Cramer, C. M. Jensen, *J. Organomet. Chem.* **2002**, *654*, 44; h) M. R. Eberhard, *Org. Lett.* **2004**, 2125; i) N. Withcombe, K. K. Hii, S. Gibson, *Tetrahedron* **2001**, *57*, 7449.

[5] a) W. A. Herrmann, C. Brossmer, K. Öfele, C. Reisinger, T. Riermeier, M. Beller, H. Fisher, *Angew. Chem.* **1995**, *107*, 1989; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844; b) A. Littke, G. C. Fu, *J. Org. Chem.* **1999**, *64*, 10; c) X. Gai, R. Grigg, I. Ramzan, V. Sridharan, S. Collard, J. Muir, *Chem. Commun.* **2000**, 2053; d) S. Gibson, D. Foster, D. Eastham, R. Tooze, D. Cole-Hamilton, *Chem. Commun.* **2001**, 779; e) M. Albrecht, G. van Koten, *Angew. Chem.* **2001**, *113*, 3866; *Angew. Chem. Int. Ed.* **2001**, *40*, 3750; f) M. E. van der Boom, D. Milstein, *Chem. Rev.* **2003**, *103*, 1759.

[6] A. F. Littke, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 6989.

[7] J. P. Stambuli, S. R. Stauffer, K. H. Shaughnessy, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 2677.

[8] a) S. Y. Cho, M. Shibasaki, *Tetrahedron: Asymmetry* **1998**, *9*, 3751; b) A. N. Cammidge, K. V. L. Crépy, *Chem. Commun.* **2000**, 1723; c) J. Yin, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12051; d) A. S. Castanet, F. Colobert, P. E. Broutin, M. Obringer, *Tetrahedron: Asymmetry* **2002**, *13*, 659; e) A. Herrbach, A. Marinetti, O. Baudoin, D. Guenard, F. Gueritte, *J. Org. Chem.* **2003**, *68*, 4897; f) A. N. Cammidge, K.

V. L. Crépy, *Tetrahedron* **2004**, *60*, 4377; g) K. Mikami, T. Miyamoto, M. Hatano, *Chem. Commun.* **2004**, 2082.

[9] a) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195; b) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem.* **2004**, *116*, 1907; *Angew. Chem., Int. Ed.* **2004**, *43*, 1871; c) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.

[10] For a review on Pd-catalyzed coupling reactions of aryl chlorides, see A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

[11] a) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550; b) A. Zapf, A. Ehrentraut, M. Beller, *Angew. Chem.* **2000**, *112*, 4315; *Angew. Chem., Int. Ed.* **2000**, *39*, 4153; c) D. A. Alonso, C. Najera, M. C. Pacheco, *J. Org. Chem.* **2002**, *67*, 5588; d) R. B. Bedford, C. S. J. Cazin, S. L. Hazelwood, *Angew. Chem.* **2002**, *114*, 4294; *Angew. Chem., Int. Ed.* **2002**, *41*, 4120; e) R. B. Bedford, S. L. Hazelwood, M. E. Limmert, *Chem. Commun.* **2002**, 2610; f) R. B. Bedford, S. L. Hazelwood, M. E. Limmert, D. A. Albisson, S. M. Draper, P. N. Scully, S. J. Coles, M. B. Hursthouse, *Chem. Eur. J.* **2003**, *9*, 3216; g) R. B. Bedford, S. L. Hazelwood, P. N. Horton, M. B. Hursthouse, *Dalton Trans.* **2003**, 4164; h) D. A. Albisson, R. B. Bedford, S. E. Lawrence, P. N. Scully, *Chem. Commun.* **1998**, 2095.

[12] a) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722; b) D. Zim, A. S. Gruber, G. Ebeling, J. Dupont, A. L. Monteiro, *Org. Lett.* **2000**, *2*, 2881; c) M. R. Netherton, C. Dai, K. Neuschutz, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 10099; d) T. J. Colacot, E. S. Gore, A. Kuber, *Organometallics* **2002**, *21*, 3301; e) J. H. Kirchhoff, M. R. Netherton, I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 13662 ; f) C.W. K. Gstöttmayr, V. P. W. Böhm, E. Herdtweck, M. Grosche, W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1421; *Angew. Chem., Int. Ed.* **2002**, *41*, 1363; g) Q.-S. Hu, Y. Lu, Z.-Y. Tang, H.-B. Yu, *J. Am. Chem. Soc.* **2003**, *125*, 2856; h) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew. Chem.* **2003**, *115*, 3818; *Angew. Chem., Int. Ed.* **2003**, *42*, 3690; i) O. Navarro, R. A. Kelly, S. P. Nolan, *J. Am. Chem. Soc.* **2003**, *125*, 16194; j) F. Y. Kwong, K. S. Chan, C. H. Yeung, A. S. C. Chan, *Chem. Commun.* **2004**, 2336; k) N. Marion, O. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101.

[13] a) E. Peris, J. A. Loch, J. Mata, R. H. Crabtree, *Chem. Commun.* **2001**, 201; b) S. Gründemann, M. Albrecht, J. A. Loch, J. W. Faller, R. H. Crabtree, *Organometallics* **2001**, *20*, 5485; c) J. A. Loch, M. Albrecht, E. Peris, J. Mata, J. W. Faller, R. H. Crabtree, *Organometallics* **2002**, *21*, 700; d) D. J. Nielsen, K. J. Cavell, B. W. Skelton, A. H. White, *Inorg. Chim. Acta* **2002**, *327*, 116; e) W. A. Herrmann, V. P. W. Böhm, C. W. K. Gstöttmayr, M. Grosche, C.-P. Reisinger, T. Weskamp, *J. Organomet. Chem.* **2001**, *617*, 616; f) C. Yang, H. M. Lee, S. P. Nolan, *Org. Lett.* **2001**, *3*, 1511; g) N. Tsoureas, A. A. Danopoulos, A. A. D. Tulloch, M. E. Light, *Organometallics* **2003**, *22*, 4750.

[14] J. L. Bolliger, O. Blacque, C. M. Frech, *Chem. Eur. J.* **2008**, *14*, 7969.

[15] J. L. Bolliger, O. Blacque, C. M. Frech, *Angew. Chem., Int. Ed.* **2007**, *46*, 6514.

[16] J. T. Singleton, *Tetrahedron* **2003**, *59*, 1837.

[17] D. Benito-Garagorri, V. Bocokic, K. Mereiter, K. Kirchner, *Organometallics* **2006**, *25*, 3817.

[18] Reviews that include catalysis of the Heck reaction by palladacycles: a) see refs [4a,b]; b) P. L. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009; c) M. Dupont, M. Pfeffer, J. Spencer, *Eur. J. Inorg. Chem.* **2001**, 1917; d) R. B. Bedford, *Chem. Commun.* **2003**, 1787; e) G. J. de Vries, *Dalton Trans.* **2006**, 421; f) D. E. Bergbreiter, P. L. Osburn, J. D. Frels, *Adv. Synth. Catal.* **2005**, *347*, 172; g) K. Yu, W. Sommer, J. M. Richardson, M. Weck, C. W. Jones, *Adv. Synth. Catal.* **2005**, *347*, 161; h) K. Yu, W. Sommer, M. Weck, C. W. Jones, *J. Catal.* **2005**, *226*, 101.

[19] a) W. A. Herrmann, V. P. W. Böhm, C.-P. Reisinger, *J. Organomet. Chem.* **1999**, *576*, 23; b) B. L. Shaw, S. D. Perera, E. A. Staley, *Chem. Commun.* **1998**, 1362.

[20] a) A. J. Arduengo, H. V. Rasika Dias, R. L. Harlow, M. Kine, *J. Am. Chem. Soc.* **1992**, *114*, 5530; b) M. S. Viciu, R. M. Kissling, E. D. Stevens, S. P. Nolan, *Org. Lett.* **2002**, *4*, 2229; c) O. Navarro, R. A. Kelly, S. P. Nolan, *J. Am. Chem. Soc.* **2003**, *125*, 16194; d) M. S. Viciu, R. A. Kelly, E. D. Stevens, F. Naud, M. Studer, S. P. Nolan, *Org. Lett.* **2003**, *5*, 1479.

[21] H. M. Lee, J. Y. Zeng, C.-H. Hu, M.-T. Lee, *Inorg. Chem.* **2004**, *43*, 6822.

[22] A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx, J. G. de Vries, *Org. Lett.* **2003**, *5*, 3285.

[23] a) W. A. Herrmann, M. Elison, J. Fischer, C. Köcher, G. R. J. Artus, *Angew. Chem.* **1995**, *107*, 2602; *Angew. Chem., Int. Ed.* **1995**, *34*, 2371; b) G. D. Frey, C. Reisinger, E. Herdtweck, W. A. Herrmann, *J. Organomet. Chem*. **2005**, *690*, 3193; c) W. A. Herrmann, K. Öfele, S. K. Schneider, E. Herdtweck, S. D. Hoffmann, *Angew. Chem.* **2006**, *118*, 3943; *Angew. Chem., Int. Ed.* **2006**, *45*, 3859.

[24] A. Schnyder, T. Aemmer, A. F. Indolese, U. Pittelkow, M. Studer, *Adv. Synth. Catal.* **2002**, *344*, 495.